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ARTICLE

Population pharmacokinetics of molnupiravir in adults with COVID-19: Lack of clinically important exposure variation across individuals

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Abstract

Effective antiviral treatments for coronavirus disease 2019 (COVID-19) are needed to reduce the morbidity and mortality associated with severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) infection, particularly in patients with risk factors for severe disease. Molnupiravir (MK-4482, EIDD-2801) is an orally administered, ribonucleoside prodrug of β-D-N4-hydroxycytidine (NHC) with submicromolar potency against SARS-CoV-2. A population pharmacokinetic (PopPK) analysis for molnupiravir exposure was conducted using 4202 NHC plasma concentrations collected in 1207 individuals from a phase I trial in healthy participants, a phase IIa trial in non-hospitalized participants with COVID-19, a phase II trial in hospitalized participants with COVID-19, and a phase II/III trial in non-hospitalized participants with COVID-19. Molnupiravir pharmacokinetics (PK) was best described by a two-compartment model with a transit-compartment absorption model and linear elimination. Molnupiravir apparent elimination clearance increased with body weight less-than-proportionally (power 0.412) and was estimated as 70.6 L/h in 80-kg individuals with a moderate interindividual variability (43.4% coefficient of variation). Additionally, effects of sex and body mass index on apparent central volume and food status and formulation on the absorption mean transit time were identified as statistically significant descriptors of variability in these PK parameters. However, none of the identified covariate effects caused clinically relevant changes in the area under the NHC concentration versus time curve between doses, the exposure metric most closely related to clinical response. Overall, the PopPK model indicates that molnupiravir

can be administered in adults without dose adjustment based on age, sex, body size, food, and mild-to-moderate renal or mild hepatic impairment.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Molnupiravir is an orally administered, ribonucleoside prodrug of β-D-N4-hydroxycytidine (NHC) with submicromolar potency against severe acute respiratory syndrome-coronavirus 2. Orally administered molnupiravir is rapidly absorbed and well-tolerated in healthy adults.

WHAT QUESTION DID THIS STUDY ADDRESS?

What are the plasma pharmacokinetic (PK) parameters of NHC in healthy adults and adults with coronavirus disease 2019 (COVID-19), and how do intrinsic and extrinsic factors influence these parameters?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

NHC concentrations following molnupiravir administration can be predicted in healthy adults and adults with COVID-19 using a linear two-compartment population PK model with absorption captured by a series of transit compartments and first-order elimination. Molnupiravir can be administered in adults without dose adjustment based on age, sex, body size, food, and mild-to-moderate renal or mild hepatic impairment.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

Predicting the parameters of NHC exposures can be used for the parallel development of viral dynamics and exposure-response models for molnupiravir.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic is a rapidly evolving and ongoing global health crisis associated with millions of COVID-19 cases and deaths, particularly in patients with risk factors for severe disease.[1] As of January 2023, the global case fatality rate for COVID-19, as reported by the World Health Organization, was ~1.02%,[2] with older people and those with comorbidities disproportionately affected.[3,4] The mean potential years of life lost per COVID-19 death is 14 and 12 years for men and women, respectively.[4]

There is an urgent need for effective treatment options that are accessible and can be readily implemented in healthcare systems globally to reduce the impact of severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) infection. Molnupiravir (MK-4482, EIDD-2801) is an orally administered, small-molecule ribonucleoside prodrug of β-D-N4-hydroxycytidine (NHC) with activity against SARS-CoV-2, coronaviruses, influenza viruses, and other RNA viruses.[5,6] Molnupiravir is hydrolyzed by esterases during absorption and first pass to deliver NHC into systemic circulation. NHC is then taken up by target cells and phosphorylated intracellularly into its pharmacologically active form, NHC triphosphate (NHC-TP), which is incorporated into viral RNA by an RNA-dependent RNA polymerase during viral replication.[6] As a result, deleterious errors accumulate throughout the viral genome that render the virus noninfectious and unable to replicate.[6] NHC-TP is ultimately cleared via conversion to cytidine and uridine, which mix with the endogenous pyrimidine nucleotide pool.

Evaluating the pharmacokinetic (PK) properties of antiviral drugs is essential to ensure drug exposures that are both safe and efficacious, with consideration given to the pathophysiologic effects associated with infection.[7] Intrinsic factors, such as body weight, age, renal function, and hepatic function, could affect drug exposure.[7] Developing population PK (PopPK) models using large datasets generated during phase II and III studies allows sources of variability in key PK parameters to be investigated to further inform dosing of therapeutic agents.[8]

This analysis was performed to develop a PopPK model for molnupiravir using NHC plasma concentrations collected in healthy adults enrolled in a phase I trial and adults with COVID-19 enrolled in three phase II efficacy and safety trials and then to extend the analysis to a pooled dataset including data collected in patients with COVID-19 enrolled in a phase III trial. The final model was used to identify and quantify the effects of intrinsic and extrinsic factors on the plasma PK of NHC to inform dosing recommendations. In addition, this model was

used to predict individual exposure metrics for developing viral dynamics and exposure-response (E-R) models.

METHODS

Study design

The data used in this analysis were collected from four studies: one phase I trial in healthy participants (MK-4482-004; ClinicalTrials.gov identifier NCT04392219; $n = 100$),[5] one phase IIa trial in non-hospitalized participants with COVID-19 (MK-4482-006; ClinicalTrials.gov identifier NCT04405570; $n = 66$),[9] one phase II trial in hospitalized participants with COVID-19 (MK-4482-001; MOVe-IN; ClinicalTrials.gov identifier NCT04575584; $n = 196$),[10] and one phase II/III trial in non-hospitalized participants with COVID-19 (MK-4482-002; MOVe-OUT; ClinicalTrials.gov identifier NCT04575597; $n = 845$).[11,12] All studies were randomized, double-blind, placebo-controlled trials of safety, tolerability, and PK of molnupiravir after oral administration. MK-4482-004 included three parts.[5] In the single ascending dose part, molnupiravir was administered in a fasted state between 50 and 1600 mg; in the food effect part, molnupiravir was given in a fasted state or after a high-fat breakfast on two separate occasions in a randomized sequence, balanced crossover design; in the multiple ascending dose part, molnupiravir was administered at 50–800 mg every 12 h (q12h) for 6 days and given in fasted state on days 1 and 6 and possibly after a meal on the other days. In MOVe-IN, MOVe-OUT (part 1), and MK-4482-006, molnupiravir was administered at 200, 400, or 800 mg q12h for 5 days to participants for treatment of COVID-19. Molnupiravir was administered at 800 mg q12h for 5 days to participants in MOVe-OUT (part 2).

All studies were conducted in compliance with the International Conference on Harmonization, in accordance with Good Clinical Practice guidelines and the US Food and Drug Administration regulations, and in line with the principles of the Declaration of Helsinki. Institutional review board approval was obtained at each participating center and all participants provided written informed consent prior to enrollment. All studies were prospectively registered on Clinicaltrials.gov prior to enrolling the first participant.

Blood sampling

In healthy participants, blood samples were collected according to a dense sampling schedule (Table S1). In participants with COVID-19, samples were collected prior to the ninth or tenth dose and at different timepoints after the associated dosing event depending on the trial: 1 and 2 h postdose in MK-4482-006; 1, 3, 5, and 8 h postdose in MOVe-IN; and 1.5 h postdose in MOVe-OUT.

Bioanalytical methods

Plasma samples were prepared by protein precipitation and NHC concentrations were determined using liquid chromatography with tandem mass spectrometry. The lower limit of quantification (LLOQ) was 5 ng/mL for samples collected in MK-4482-004 and MK-4482-006, and 1 ng/mL for samples collected in MOVe-IN and MOVe-OUT. Prior to modeling, all dose amounts and NHC concentrations were converted to molar units using the molecular masses of molnupiravir (329.31 Da) and NHC (259.2 Da).

Population PK model development

PopPK modeling was performed using data from all participants who received molnupiravir and contributed at least one plasma sample with a measurable concentration of NHC. Nonlinear mixed effects modeling was applied to analyze NHC concentration data using the first-order conditional estimation with the interaction estimation method. Measurements associated with duplicate sampling date and time or missing or uncertain dosing history or collected in participants with missing and non-imputable covariate information were excluded during modeling.

Model development was performed in three separate stages. A base structural model of molnupiravir PK was initially selected after testing a large variety of absorption and disposition models based on the dense phase I data (stage 1). This PopPK model was then refined based on inclusion of data from the phase II trials (MK-4482-006, MOVe-IN, and MOVe-OUT [part 1]) and a formal covariate search was performed (stage 2). Finally, the full PopPK model was extended to describe the sparse data from the phase III part of MOVe-OUT, including refinement of the absorption model and covariate re-assessment (stage 3).

Different structural models were applied to characterize NHC absorption and disposition, based on the results of exploratory data analysis and model development steps. The models were described by the estimation of mean structural model parameters, magnitude of interindividual variability (IIV), and/or inter-occasion variability (IOV) in these parameters and magnitude of residual variability (RV). Because molnupiravir data were only

collected after oral dosing, the models were described in terms of apparent disposition parameters (e.g., apparent elimination clearance [CL/F]). The effect of a high-fat diet on molnupiravir absorption was examined at stage 1. Variability in PK parameters generally assumed to be log-normal models and different RV models (constant coefficient of variation [CV], additive plus constant CV, and log models) were tested to capture the remaining within-participant variability.

In the phase II and III trials, information about whether patients with COVID-19 received molnupiravir dosing after overnight fast or a (potential high-fat) meal around the time of blood sampling was not collected. Therefore, as part of the structural model refinement using the phase II data (stage 2), mixture modeling was applied to determine patient food status, which was, thereafter, hard-coded into the analysis dataset. The influence of covariates on selected parameters was then evaluated using a systematic univariate screening approach with forward covariate selection and backward elimination.[13] A covariate effect was included in the model if it reduced the minimum objective function value by a statistically significant amount ($\alpha = 0.01$ for forward selection and $\alpha = 0.001$ for backward elimination) and the IIV in the parameter of interest decreased (during forward selection only). After each of the forward selection and backward elimination steps, the IIV and RV models were re-examined for any remaining biases and possible adjustment. The effect of hepatic function on NHC disposition was then tested using modified Child-Pugh criteria (see Table S2), as this variable was added to the analysis dataset following formal covariate screening. Hepatic function was not explicitly captured in the clinical database, so the degree of hepatic impairment was approximated using the modified Child-Pugh score based on reported laboratory values for total bilirubin and albumin, whereas encephalopathy, ascites, and international normalized ratio were assumed to be normal as these parameters were not collected in the clinical dataset. After inclusion of phase III data (stage 3), the PopPK model was further refined by re-examination of the absorption model and re-test of the previously identified covariates through a second round of backward elimination ($\alpha = 0.001$).

The predictive performance of the PopPK model was evaluated using a simulation-based, prediction-corrected visual predictive check (VPC) method.[14] Plasma NHC concentrations were simulated to achieve greater than or equal to 10,000 participants per data stratum. The 5th, 50th (median), and 95th percentiles of the distributions of simulated and observed concentrations were calculated, plotted versus time, and compared visually.

In another stochastic simulation using the final model and a population of 1000 virtual subjects with characteristics resampled from the analysis dataset, full model-predicted PK profiles were compared with the observed kinetics of NHC in participants with COVID-19.

Assessment of clinical relevance of intrinsic and extrinsic factors' effects on PK

The clinical relevance of the effects of intrinsic and extrinsic factors on NHC plasma PK was evaluated in the final PopPK model using covariate data from participants included in the analysis dataset and their individual Bayesian estimates of PK parameters. Simulations assumed hypothetical 800 mg q12h molnupiravir dosing for 5 days for all individuals in the analysis dataset and the clinical relevance of the predicted intrinsic and extrinsic factor effects was judged based on a comparison of whether the full 90% confidence interval (CI) of the associated geometric mean ratio (GMR) for the area under the concentration–time curve (AUC) from 0 to 12 h after dosing ($AUC_{0–12}$) fell within clinical comparability bounds of 0.7–2.0 set based upon E-R analyses for efficacy and safety. The exposure metric $AUC_{0–12}$ was used for these assessments as it has the strongest association with clinical response, as shown in previous E-R analyses.[15] The 0.7–2.0 range corresponds to plasma NHC $AUC_{0–12}$ of ~23,800–68,000 nmol·h/L with molnupiravir 800 mg q12h. In the phase III portion of MOVe-OUT, a higher rate of hospitalization was observed in participants with exposures in the lowest exposure octile (AUC median: 21,020 and 95% CI: 15,650–23,780 nmol·h/L). Although E-R analysis[15] demonstrated that this higher rate of hospitalization was primarily due to other influential factors, such as higher prevalence of obesity and diabetes in this subset, and that meaningful drug benefit would be obtained at exposures within the range of the lowest exposure octile, the lower clinical bound of 23,800 nmol·h/L was selected so that all subgroups maintain mean exposures above those observed in the lowest exposure octile of MOVe-OUT. The upper bound of 2.0 ensures that subpopulations are maintained within the range of clinical experience at 800 mg because 48 participants have achieved plasma NHC $AUC_{0–12}$ greater than this threshold in the molnupiravir clinical studies without notable alteration of the safety and tolerability profiles. Of note, the clinical relevance range defined is relevant for comparison to geometric mean and 90% CI values for subpopulations and should not be used on an individual basis as individual exposures are expected to range more widely.

Software

All exploratory analyses and presentations of data were performed using SAS version 9.4 (SAS Institute), KIWI version 4 (Simulation Plus, Cognigen Division),[16] and R version 3.6.1 (R Foundation for Statistical Computing). Population modeling was performed using NONMEM (ICON), version 7, level 3,[17] on an Intel cluster with the Linux operating system (Linus Torvalds, open-source operating system).

RESULTS

The overall population included 100 healthy participants, 196 hospitalized participants with COVID-19, and 911 non-hospitalized patients with COVID-19, including 651 patients from the phase III portion of MOVe-OUT. A total of 4847 plasma NHC sample records were collected from participants who received molnupiravir, and 4202 were included in the analysis (see Table S3 for more information on reasons why samples were excluded). The dataset comprised 624 (51.7%) men and 583 (48.3%) women. The majority of participants were White (66.7%). Participants had a median (range) age of 46 (18–91) years and median (range) body weight was 85 (36.1–172) kg. Almost half (48.1%) of the participants had mild renal impairment (estimated glomerular filtration rate [eGFR]: 60–89 mL/min/1.73 m^2), and 7.0% had moderate renal impairment (eGFR: 30–59 mL/min/1.73 m^2). Demographics and baseline characteristics are presented in Table 1.

Participants with COVID-19 were generally older (median age of 46 years, compared with 35.5 years for healthy participants) and had a higher median body mass index (BMI: 30.9 kg/m^2 vs. 25 kg/m^2). Hepatic impairment was only observed in participants with COVID-19 (5.4% [60/1107] with mild impairment and 0.3% [3/1107] with moderate impairment), and moderate renal impairment was also more prevalent in participants with COVID-19 compared with healthy participants (7.5% [83/1107] vs. 1% [1/100]). Approximately 25% of participants hospitalized with COVID-19 had taken or were receiving remdesivir when treatment with molnupiravir was initiated. Remdesivir was not administered to any non-hospitalized participants.

Exploratory PK analysis

The size of the PK analysis dataset increased as the analysis proceeded from 1996 samples in 99 healthy participants at stage 1 (one outlier individual was temporarily excluded), to 3474 samples from 554 individuals administered molnupiravir at stage 2, to 4750 samples from 1212 individuals at stage 3 (Table S3). Participants with COVID-19 contributed fewer samples per participant ($n = 1–5$) compared with healthy participants ($n = 7–26$), resulting in 72.8% of the study population participants contributing less than or equal to two samples, 18.9% contributing three to five samples, and only 8.3% contributing greater than five samples.

Overall, 4202 (88%) of the 4750 available postdose samples in participants assigned to molnupiravir had NHC concentrations within the assay quantification range. Most of the non-quantifiable concentrations were obtained in MK-4482-004 at lower doses (≤200 mg) where intensive sampling continued after the profiles fell below the LLOQ. Less than 3% of the data collected in the phase II and phase III trials were below the LLOQ. All concentrations below the LLOQ were excluded after checking that they did not influence model estimates, resulting in the sample counts provided here. After administering molnupiravir in capsule formulation, NHC plasma concentrations increased rapidly, with maximum concentrations (C_{max}) being reached within 1–2 h, before decreasing in a bi-exponential manner. The rate of elimination appeared to be consistent across dose groups. A high-fat breakfast also lowered and delayed peak concentrations. Median NHC plasma concentrations were generally comparable between healthy participants and those with COVID-19 following the last dose of molnupiravir in all trials, although greater variability was observed among patients with COVID-19.

Base structural model development using phase I (stage 1) and phase II data (stage 2)

Initial modeling runs indicated that a two-compartment model with linear elimination better described the data from healthy participants in combination with an absorption model defined by a mathematical approximation of a series of transit compartments (Figure 1a) rather than by a first-order process. However, this model was found to be unstable when applied to the stage 2 analysis population, and it was not possible to progress with covariate analysis due to early termination issues, rounding errors, and/or higher final gradient values. Instead, a simpler absorption model (Figure 1b) was implemented in which molnupiravir is assumed to enter a depot compartment at a constant zero-order rate for an estimated duration (D1), prior to a first-order transfer to the central compartment. Both models exhibited similar kinetic properties (Figure S1). A high-fat diet significantly increased D1 but did not affect the relative bioavailability of molnupiravir.

In patients with COVID-19, data on food status were absent. However, variability in the data, and the absence of

TABLE 1 Demographics and baseline characteristics.

	Participants with COVID-19 infection				Healthy adults	
	MOVe-IN	MOVe-OUT		MK-4482-006	MK-4482-004	
	Phase II ($n=196$)	Phase II[a] ($n=194$)	Phase III ($n=651$)	Phase IIa ($n=66$)	Phase I ($n=100$)	Overall ($N=1207$)
Age, year						
Mean (SD)	56.3 (13.9)	48.8 (14.4)	44.3 (14.6)	41.2 (15.7)	38.8 (13.3)	46.4 (15.3)
Median	56	50	42	37	35.5	46
Minimum, maximum	19, 91	18, 81	18, 90	19, 82	20, 60	18, 91
Sex, *n* (%)						
Male	113 (57.7)	95 (49.0)	301 (46.2)	32 (48.5)	83 (83.0)	624 (51.7)
Female	83 (42.3)	99 (51.0)	350 (53.8)	34 (51.5)	17 (17.0)	583 (48.3)
BMI, kg/m^2						
Mean (SD)	30.1 (6.1)	29.7 (6.1)	31.9 (5.9)	27.2 (5.0)	24.8 (2.8)	30.4 (6.1)
Median	28.8	29.7	31.6	26.6	25	30.4
Minimum, maximum	17.5, 48.8	18.1, 49.1	14.3, 68.6	19.6, 43.9	19, 29.9	14.3, 68.6
Body weight, kg						
Mean (SD)	85.9 (19.8)	84.1 (18.4)	88.3 (18.3)	80.8 (18.3)	75.8 (10.8)	85.8 (18.4)
Median	84.1	81.8	88	74.6	75.8	85
Minimum, maximum	50.7, 172	48, 134	36.1, 158	51.9, 131	48, 101	36.1, 172
Racial classification, *n* (%)						
White	144 (73.5)	145 (74.7)	367 (56.4)	56 (84.8)	93 (93.0)	805 (66.7)
Black or African American	7 (3.6)	14 (7.2)	33 (5.1)	5 (7.6)	4 (4.0)	63 (5.2)
Asian	18 (9.2)	1 (0.5)	22 (3.4)	2 (3.0)	0 (0)	43 (3.6)
Native American or Alaska Native	4 (2.0)	5 (2.6)	57 (8.8)	0 (0)	0 (0)	66 (5.5)
Hawaiian or Pacific Islander	1 (0.5)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.1)
Asian	18 (9.2)	1 (0.5)	22 (3.4)	0 (0)	2 (3.03)	43 (3.6)
Other	22 (11.2)	29 (14.9)	172 (26.4)	3 (4.6)	3 (3.0)	229 (19.0)
Ethnicity, *n* (%)						
Non-Hispanic or Latino	118 (60.2)	131 (67.5)	322 (49.5)	44 (66.7)	99 (99.0)	714 (59.2)
Hispanic or Latino	78 (39.8)	63 (32.5)	329 (50.5)	22 (33.3)	1 (1.0)	493 (40.8)
Geographic region, *n* (%)						
North America	26 (13.3)	66 (34.0)	89 (13.7)	66 (100)	0 (0)	247 (20.5)
Europe	99 (50.5)	88 (45.4)	208 (32.0)	0 (0)	100 (100)	495 (41.0)
Latin America	9 (4.6)	0 (0)	17 (2.6)	0 (0)	0 (0)	26 (2.2)
Asia Pacific	62 (31.6)	34 (17.5)	258 (39.6)	0 (0)	0 (0)	354 (29.3)
Africa	0 (0)	6 (3.1)	79 (12.1)	0 (0)	0 (0)	85 (7.0)
Hepatic function,[b] *n* (%)						
Normal	149 (76.0)	191 (98.5)	641 (98.5)	63 (95.5)	100 (100)	1144 (94.8)
Mild impairment	45 (23.0)	21 (1.0)	10 (1.5)	3 (4.6)	0 (0)	60 (5.0)
Moderate impairment	2 (1.0)	1 (0.5)	0 (0)	0 (0)	0 (0)	3 (0.2)

TABLE 1 (Continued)

	Participants with COVID-19 infection				Healthy adults	
	MOVe-IN	MOVe-OUT		MK-4482-006	MK-4482-004	
	Phase II ($n=196$)	Phase II[a] ($n=194$)	Phase III ($n=651$)	Phase IIa ($n=66$)	Phase I ($n=100$)	Overall ($N=1207$)
Renal function,[c] *n* (%)						
Normal	87 (44.4)	83 (42.8)	290 (44.5)	36 (54.5)	47 (47.0)	543 (45.0)
Mild impairment	82 (41.8)	97 (50.0)	322 (49.5)	27 (40.9)	52 (52.0)	580 (48.1)
Moderate impairment	27 (13.8)	14 (7.2)	39 (6.0)	3 (4.6)	1 (1)	84 (7.0)
Formulation, *n* (%)						
Oral solution	0 (0)	0 (0)	0 (0)	0 (0)	36 (36.0)	36 (3.0)
Capsule	196 (100)	194 (100)	651 (100)	66 (100)	64 (64.0)	1171 (97.0)
Food status collection, *n* (%)						
No	196 (100)	194 (100)	651 (100)	66 (100)	0 (0)	1107 (91.7)
Yes	0 (0)	0 (0)	0 (0)	0 (0)	100 (100)	100 (8.3)
Study population, *n* (%)						
Healthy	0 (0)	0 (0)	0 (0)	0 (0)	100 (100)	100 (8.3)
Non-hospitalized	0 (0)	194 (100)	651 (100)	66 (100)	0 (0)	911 (75.5)
Hospitalized	196 (100)	0 (0)	0 (0)	0 (0)	0 (0)	196 (16.2)
Baseline remdesivir use, *n* (%)						
No	148 (75.5)	194 (100)	651 (100)	66 (100)	100 (100)	1159 (96.0)
Yes	48 (24.5)	0 (0)	0 (0)	0 (0)	0 (0)	48 (4.0)

Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019.

[a]Data from seven participants became available when the phase III part of this trial completed.

[b]Modified Child-Pugh criteria (mild impairment, class B; moderate impairment, class C).

[c]Based upon estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease equation (normal, ≥90 mL/min/1.73 m^2; mild impairment 60–89 mL/min/1.73 m^2; moderate impairment, 30–59 mL/min/1.73 m^2).[19]

data on food status, suggested that some patients were dosed after a high-fat meal. Application of mixture modeling stabilized the model and decreased the IIV in D1 from greater than 100 %CV to ~50 %CV. Following a small-scale sensitivity analysis, the fraction of participants with an unknown food status being considered to have consumed a high-fat meal was fixed to 25%. Additional refinements conducted at stage 2 of analysis included a reduced IIV structure (IIV only on CL/F) for participants who contributed fewer than three NHC measurements, distinct residual variability models being estimated for the phase I and II studies, and three data points with absolute values of conditional weighted residuals more than five being excluded.

During covariate screening, the effects of body weight on CL/F, sex, and BMI on the apparent central volume of distribution (V_C/F), formulation and hospitalization status on D1 were included in the model. All parameters of the selected base structural models were well estimated (relative standard error [RSE] <21%). Goodness-of-fit plots (data not shown) and a VPC (Figure S2) suggested that this model described the data reasonably well across all studies.

Base model refinement using phase III data (stage 3)

Attempts to re-estimate the stage 2 model after incorporating the phase III dataset were not successful, even after fixing the absorption parameters to estimates obtained in models fitted to the densely sampled data only. Reverting the absorption model to a transit compartment structure (Figure 1a) resolved this issue. Food, formulation, and hospitalization effects, and IIV associated with D1 in the prior model, were assumed to be associated with the mean absorption transit time (MTT). Additionally, variability in MTT was modeled using IOV after testing that IIV in MTT reduced to zero when associated with IOV. Covariate effects associated with disposition parameters were assumed to remain unaffected by the change in the absorption model. Following this refinement of the absorption model, the shift in MTT in hospitalized patients was close to 0 and poorly estimated (RSE: 87.2%). Similar to the stage 2 model, the variability structure was reduced (to IIV only on CL/F) for participants who contributed fewer

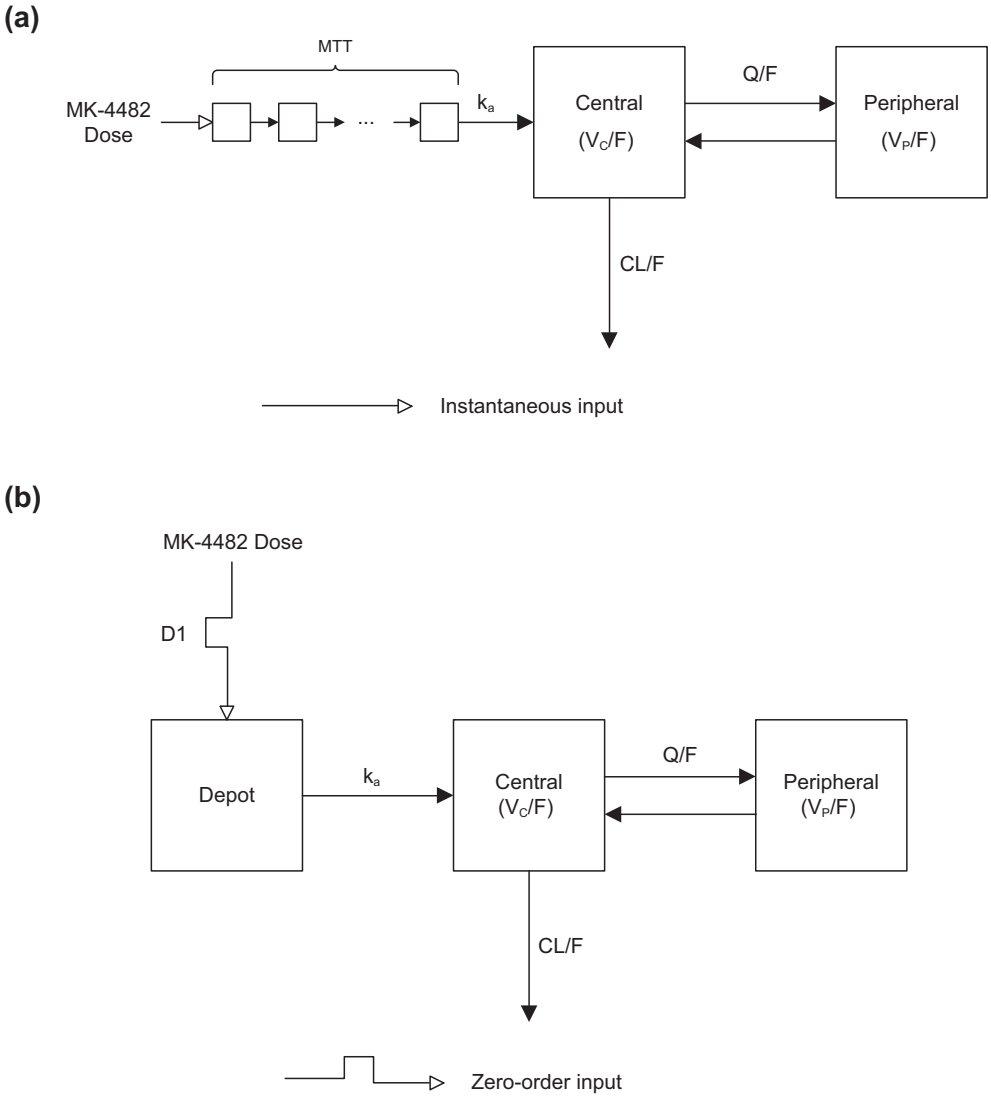

FIGURE 1 Schematic of the pharmacokinetic models for plasma NHC following molnupiravir administration used in (a) analysis stages 1 and 3 and (b) stage 2. CL/F, apparent elimination clearance; D1, duration of the zero-order absorption process; k_a, first-order absorption rate constant; MTT, mean absorption transit time; NHC, β-D-N4-hydroxycytidine; Q/F, apparent distribution clearance; V_C/F, apparent central volume; V_P/F, apparent peripheral volume.

than three NHC measurements, as these participants had insufficient data to estimate two IIV and one IOV terms.

When performing the stepwise backward elimination analysis, all covariate–parameter relationships, except the shift in MTT for hospitalized patients, were found to be statistically significant and, therefore, remained in the model. The covariate effects included in the final model as statistically significant predictors of the PK parameters were: less-than-proportional power function of body weight on CL/F, less-than-proportional power function of BMI on V_C/F, 33% decrease in V_C/F in women compared with men, 422% increase in MTT following a high-fat meal compared with fasting or a standard meal, and 61.6% decrease in MTT for oral solution compared with capsule or suspension.

Final model

The model resulting from the stepwise backward elimination and removal of the shift in MTT for the hospitalized patient parameter was selected as the final PK model (Table 2). All parameters were estimated precisely (RSE: <24.1%) and without correlation. VPC plots (Figure 2, Figure S4) and goodness-of-fit plots (Figure S3) indicated that this model described the data equally as well as the stage 2 model. The median and variance of predicted NHC concentrations over time generally tracked well with observed values in participants with COVID-19, with a slight underprediction at the lower end of the concentration range. Observed NHC plasma concentration data in all

dose groups of participants with COVID-19 were well-described by the final PopPK model (Figure S5).

Clinical relevance of covariates on NHC PK

The impact of covariate effects included in the final plasma NHC PK model and variables not included in the model were evaluated based on the simulated GMR relationships for $AUC_{0–12}$, predicted assuming a hypothetical molnupiravir dosing regimen of 800 mg q12h for 5 days. No clinically important change in exposure was identified for any intrinsic or extrinsic factor (e.g., body weight, age, sex, race, renal function, and hepatic function), indicating that the same 800 mg q12h dose is appropriate for all subpopulations (Figure 3, Figures S6 and S7). Simulations of GMRs for trough concentration (C_{trough}) and C_{max} are provided for completeness but were not used for evaluation of clinical relevance (Figures S8 and S9). To further investigate any effect of racial classification, predicted NHC $AUC_{0–12}$ values for Japanese participants were compared with those of non-Japanese participants with similar body weight (Figure S10). No clear difference in exposure for Japanese participants was observed after accounting for body weight.

DISCUSSION

Molnupiravir is orally administered and is generally not detectable in plasma due to rapid hydrolysis to NHC during absorption and first-pass metabolism. NHC was evaluated across phase I, phase II, and phase II/III trials as the primary circulating analyte for molnupiravir. NHC exhibits linear, time-independent PK with approximately dose-proportionate increases across the dose range studied.[5] Although the primary circulating analyte NHC is subsequently taken up into cells and phosphorylated to the active triphosphate metabolite NHC-TP, plasma NHC is an appropriate target for population PK analysis as it was evaluated across phase I, phase II, and phase II/III trials and collection of NHC-TP data is not practical in a clinical setting.[6] Furthermore, the AUC of NHC in the plasma was a strong and consistent predictor of NHC-TP exposures in peripheral blood monocytes, a surrogate for the site of action (Merck & Co., Inc., Rahway, NJ, USA, unpublished data). Consistent with an interpretation of NHC AUC as the driver for uptake and conversion of NHC to NHC-TP intracellularly, the strength of the E-R relationships established for NHC AUC and for clinical outcomes, as well as for virologic response, were lessened or absent for other NHC PK measures, such as C_{trough} (Merck & Co., Inc., Rahway, NJ, USA, unpublished data).[18] As such, the focus of this PopPK analysis and intrinsic/extrinsic factor evaluation was NHC $AUC_{0–12}$ in the plasma.

In this analysis, a PopPK model was developed using NHC plasma concentration data collected after single and repeated molnupiravir administration in 1207 healthy individuals and patients with COVID-19, which substantially extends the characterization of PK beyond the published phase I experience.[5] A two-compartment model with linear absorption and elimination was found to reliably predict plasma PK of NHC. CL/F, the parameter determining $AUC_{0–12}$, was characterized as 70.6 L/h with a moderate level of intersubject variability (43.4 %CV). The only statistically significant covariate on CL/F was a less-than-proportional power relationship with body weight. Additionally, covariate effects of sex and BMI on V_C/F and food status and formulation on the absorption MTT were identified. Food status and formulation were not found to influence the extent of molnupiravir bioavailability.

The structure of the disposition portion of the PK model remained the same across the three stages of model development; however, the absorption process was characterized using transit compartments in the modeling stages 1 and 3 and as a sequential zero and first order transfer in the modeling stage 2. Both functions allow the drug to be absorbed according to a prototypical "S" shape function of time (see Figure S1), but the model based on transit compartments is generally more flexible and was judged to better describe absorption kinetics, which are notable for a fairly variable time to maximum concentration (T_{max}). The large change in MTT with food status affected T_{max} and C_{max}, but the extent of absorption, and therefore AUC, remained consistent across participants regardless of food status. Because NHC $AUC_{0–12}$ is the exposure metric expected to be most closely related to efficacy and safety, molnupiravir may be administered without regard to food, consistent with the dosing instructions for phase II and III trials.

Simulation of the typical PK profile using the final model indicates that NHC concentration is expected to peak at 11,400 nmol/L ~1.5 h after the last dose, with half-lives of 0.6 and 16.5 h for the first and second phases of disposition, respectively, based on a reference individual defined as a non-hospitalized man with a 78 kg body weight and BMI of 28 kg/m^2 receiving a 5-day course of molnupiravir 800 mg twice daily.

Measures of body size (body weight and BMI) were the most influential intrinsic factors identified in the PopPK analysis in both covariate testing and forest plots of predicted effects on $AUC_{0–12}$. The highest BMI category (>40 kg/m^2; $n = 83$) was the subpopulation associated with the lowest NHC AUC of all the intrinsic factor groups examined; however, the GMR (90% CI) of 0.787 (0.73, 0.848) in this population was contained within the

TABLE 2 Parameter estimates and standard errors for the final refined NHC pharmacokinetic model.

Parameter	Final parameter estimate		Magnitude of variability	
	Population mean	%RSE	Final estimate	%RSE
CL/F				
Apparent central clearance in 80 kg participants, L/h	70.6	1.97	43.4 %CV	8.99
Power of body weight effect	0.412	14.0		
V_C/F				
Apparent central volume in 28 kg/m^2 BMI male participants, L	63.9	5.07	62.9 %CV	24.1
Proportional shift in female participants	−0.330	11.8		
Power of BMI effect	0.997	13.1		
Q/F				
Apparent distribution clearance, L/h	2.99	5.70	NE	NA
V_P/F				
Apparent peripheral volume, L	68.3	14.6	NE	NA
k_a				
First-order absorption rate constant, 1/h	0.797	2.57	NE	NA
MTT				
Mean absorption transit time, h	0.435	5.39	NE	NA
Proportional shift due to high-fat meal	4.22	6.29		
Proportional shift in oral solution	−0.616	5.49		
NN				
Number of transit compartments	7.84	16.5	NE	NA
F1				
Relative bioavailability	1.00	Fixed	NE	NA
IOV in MTT[a]	NA	NA	39.8 %CV	17.6
Residual variability				
Phase I trials	0.0652	11.9	25.5 %CV	NA
Phase II/III trials	0.247	4.00	49.7 %CV	NA

Note: The different occasions for IOV in MTT were labeled as occasion 1 and occasion 2. Participants were assumed to have only one occasion for IOV in MTT, except those enrolled in the food effect and MAD part of MK-4482-004. Shrinkage estimates: 9.3% for IIV in CL, 27.9% for IIV in V_C, 27.6% for IOV in MTT: occasion 1, and 7.8% for IOV in MTT: occasion 2.

Abbreviations: BMI, body mass index; CL, clearance; %CV, coefficient of variation expressed as a percent; F, bioavailability; F1, relative bioavailability; IIV, interindividual variability; IOV, inter-occasion variability; k_a, first-order absorption rate constant; MAD, multiple ascending dose; MTT, mean absorption transit time; NA, not applicable; NE, not estimated; NHC, β-D-N4-hydroxycytidine; NN, number of transit compartments; Q, distribution clearance; %RSE, relative standard error expressed as a percent, V_C, central volume; V_P, peripheral volume.

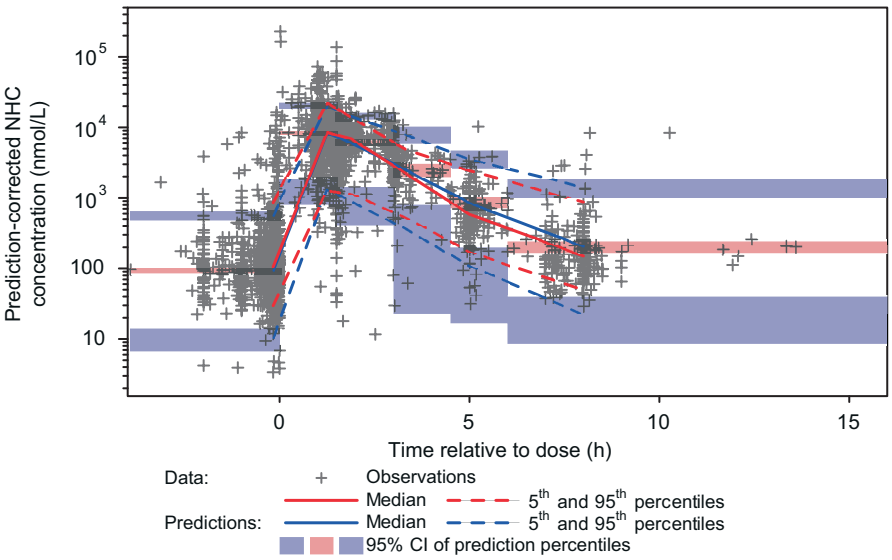

FIGURE 2 Visual predictive check plot for the final stage 3 pharmacokinetic model in participants with COVID-19. Medians and percentiles are plotted at the median time for each interval of time relative to dose. CI, confidence interval; COVID-19, coronavirus disease 2019; NHC, β-D-N4-hydroxycytidine.

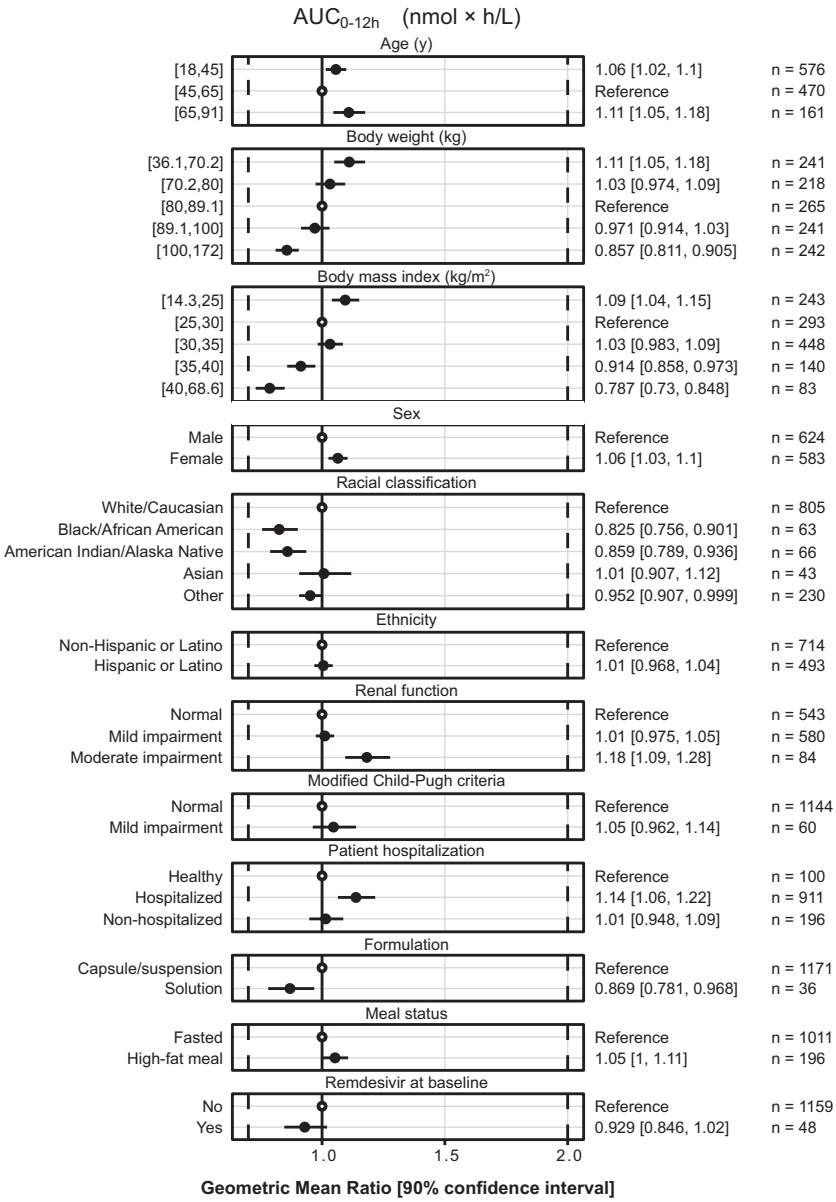

FIGURE 3 Forest plot of GMRs (90% CI) for stage 3 model-predicted AUC_{0-12} after molnupiravir 800 mg q12h. *n* is the number of participants in each group; [or] indicates respective end point is included in the interval; (or) indicates respective end point is not included in the interval. AUC_{0-12}, area under the NHC concentration versus time curve from 0 to 12 h postdose; CI, confidence interval; GMR, geometric mean ratio; NHC, β-D-N4-hydroxycytidine; q12h, every 12 h.

0.7–2.0 bounds of clinical significance. These findings are further supported by efficacy subgroup analyses, which demonstrated no clear reduction in efficacy relating to BMI.[11] No dose adjustment for any subpopulation based on body weight or BMI is recommended. No clinically relevant PK effects were identified for subpopulations based on racial or ethnic classifications. Trends toward lower exposures in Black/African American (GMR: 0.825) and American Indian/Alaska Native (GMR: 0.86) categories appeared to be driven by higher body weights/BMI in these subpopulations. No meaningful difference in exposures was identified for Asian participants (GMR: 1.01). Age was not a statistically significant covariate and predicted NHC exposures were consistent even in the oldest participants (Figure 3). Women typically had a 15% higher C_{max} than men; however, there was no clinically relevant difference in NHC AUC_{0-12} between men and women.

Renal impairment was not identified as a statistically significant covariate in the analysis, which included 48% and 7% of participants with mild or moderate renal impairment, respectively. The predicted modest 18% AUC_{0-12} increase with moderate renal impairment was not considered to be clinically relevant. Whereas it is acknowledged that the modified Child-Pugh score may underestimate the true number of participants with higher degrees of hepatic impairment, the available data in participants with mild ($n=60$) and moderate ($n=3$) hepatic impairment did not identify a distinguishable trend in NHC exposures with hepatic dysfunction. Overall, no dose adjustment for any intrinsic or extrinsic factors evaluated in this analysis appears necessary.

Limitations

Our analyses are limited by a small number of participants in some subpopulations, including those with moderate hepatic impairment. Food status was not collected for participants in phase II and III trials, requiring mixture modeling to assign a food status. Because food status was not documented for any patients with COVID-19, assignment of fed/fasted status based on the mixture model may be confounded by disease status or other unknown covariates. This model-based assignment could have impacted the estimation of other covariate effects. Furthermore, it was possible to estimate IIV or IOV on CL/F, V_C/F, and MTT in approximately a third of the analysis population that was sampled during the absorption phase of NHC, although only the IIV in CL/F could be estimated in the rest of the analysis population with more sparse data. Finally, the selected model does not include any allometric scaling of apparent distribution clearance and apparent peripheral volume, limiting its use in the pediatric population.

CONCLUSIONS

NHC concentrations following molnupiravir administration were well-characterized in healthy adults and adults with COVID-19 using a PopPK model comprising a linear two-compartment model with absorption captured by a series of transit compartments and first-order elimination. Overall, findings from the analysis suggest that molnupiravir could be administered in adults without dose adjustment based on age, sex, body weight, BMI, food, and mild-to-moderate renal or mild hepatic impairment.

AUTHOR CONTRIBUTIONS

S.B., Y.C., A.C., R.B., B.M.M., W.G., S.S., R.H., S.K., B.J., M.M., W.P., G.P., W.H., C.D., M.L.B., M.G.J., A.P., M.L.R., and J.A.S. wrote the manuscript. S.B., A.C., W.G., S.S., R.H., W.P., G.P., W.H., M.L.B., M.G.J., A.P., M.L.R., and J.A.S designed the research. S.B., Y.C., R.B., W.G., S.S., R.H., B.M.M., M.L.B., M.G.J., and M.L.R. performed the research. S.B., Y.C., A.C., W.G., S.R., S.S., R.H., S.K., B.J., M.M., G.P., W.H., C.D., A.P., M.L.R., and J.A.S. analyzed the data.

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CONFLICT OF INTEREST STATEMENT

A.C., R.B., B.M.M., M.M., C.D., M.L.B., M.G.J., A.P., M.L.R., and J.A.S. are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, who may own stock and/or hold stock options in Merck & Co., Inc., Rahway, NJ, USA. Y.C. and W.G. were employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, at the time the study was conducted. W.P. is an employee of Ridgeback Biotherapeutics LP, Miami, FL, USA; listed as an inventor on patent applications relating to molnupiravir and has consulted for Drug Innovation Ventures at Emory University and Emory Institute of Drug Development, Atlanta, GA, USA. G.P. has received

consulting fees from Merck & Co., Inc., Rahway, NJ, USA; listed as an inventor on patent applications relating to molnupiravir and receives royalties from molnupiravir sales. W.H. is an owner and cofounder and advisor to Ridgeback Biotherapeutics LP, Miami, FL, USA; listed as an inventor on patent applications relating to molnupiravir and owns stock and/or holds stock options in Merck & Co., Inc., Rahway, NJ, USA. S.B., S.R., S.S., R.H., S.K., and B.J. are current or former employees and may own stock and/or hold stock options of Simulations Plus, Cognigen Division, which was contracted by Merck & Co., Inc., Rahway, NJ, USA, to perform the analysis reported here.

DATA AVAILABILITY STATEMENT

The data sharing policy, including restrictions, of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA is available at https://engagezone.msd.com/ds_documentation.php. Requests for access to the clinical study data can be submitted through the Engage Zone site or via email to the Data Access mailbox.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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